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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
CHANG, CELIA C	
ART UNIT	**PAPER NUMBER**
1625	

DATE MAILED: 04/18/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/004,422	PEYMAN ET AL.	
	Examiner	Art Unit	
	Celia Chang	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *03 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's election with traverse of Group I, claims 4-6 wherein D is carbon and those subject matter of claims 1-3, 7-13 reading on D is carbon and the species of example 2, p.34 in Paper No. 8, dated mar. 13, 2003 is acknowledged. The traversal is on the grounds that the examiner has not shown that examination will result in a serious burden. This is not found persuasive because it has been show with citation that examination of all the groups would be a serious since a reference anticipates compounds wherein D is N (group II) unpatentable would not necessarily renders compounds of other groups obvious. Applicants were advised that "Should applicant traverse on the ground that the groups and species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing that the groups and species to be obvious variants or clearly admit on the record that this is the case" but without making such submission or admission of the record.

The requirement is still deemed proper and is therefore made FINAL.

It is further noted that when D is N and ringD is bicyclic, the compounds are thrombin inhibitors (CA 136:210039); when D is N, and ringD is monoheteroatom and monocyclic 5-membered, the compounds are antibiotics (see CA120:269926); when D is N, ringD is multiple heteroatoms monocyclic 5-membered, the compounds are hypolipemic agent (CA 91:193292); when D is C, ringD is monocyclic cycloalkyl, the compounds are dopamine receptor ligands (CA137:201331); when D is O, the compounds are GnRH inhibitor (see CA 132:279106). Therefore, not only the compounds are independent and distinct for each groups, the species are further evidenced to be distinct since each individual core represents a different utility.

Therefore, based on the group and species election, the following subject matter is examined:

V is formula IIa, with all variables defined as in claim 1,

 is phenyl, optionally substituted by R^1,

R0, Q, Q', X, R^1 and R^{10} are as defined in claim 1.

The remaining subject matter are hereby withdrawn from consideration per 37 CFR 1.142(b).

2. Claims 1-6 and 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Please note that each claim can only have "one" period (see MPEP 608.01(m)). The instant claims 1-6 contain multiple periods and indents which are very confusing. It is recommended that all the numerical system be deleted with proper comma and semicolon placed in appropriate phrases to mark each group of Markush definition for each variable.

It is very confusing as to the  structure because it is unclear as to what it means, since it has 10 ring bond, it looks like a 10 membered single ring with  as the only variable in it but it also referred to in formula III to be bicyclic, heterocyclic, heterocaryl etc. Such notation is self-conflicting i.e. a single ring with bonding at adjacent position and a bicyclic ring with variable bonding arrangement can not be represented by this notation. It is recommended that since the elected invention is  is phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^1, the structural notation be made consistent with the description.

Claim 8 is self-conflicting since it is a pharmaceutical composition without quantitative limitation. Please note that a pharmaceutical composition can not be ineffective or toxic, therefore, the quantitative relationship of "therapeutically effective amount" of an active ingredient must be incorporated.

3. Claims 9-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 9 is confusing as to what does the term "for inhibition of factor Xa....." is referring to. If it is referring to the intended use, then this is a duplicate of claim 8. (see MPEP 612.03(k), one of the duplicate claim should be canceled) If this is referring to containing a factor Xa....inhibitory effective amount, then such quantitative relationship should be incorporated into the claim.

Claim 10 is very confusing as to what is the scope of the claims because some conditions are pathology which is treatable by factor Xa inhibition while other are response which may or

may not be pathological. For example, inflammatory "response" is not a disease and treating inflammation and treating inflammatory response are not identical.

Further, while anticoagulants is administered to post tansluminal coronary angioplactic surgery patients, such administration is not treating coronary disease which was treated by the angioplastic surgery. Therefore, it is recommended that "what" is the method, steps, targets, dosage be explicitly delineated in the claim.

In addition the term "associated with" is indefinite how associate is associated with?

Further, the claim contains the term "for example" which is a relative term which renders the claim indefinite. The term "for example" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

4. Claim 10 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for method or treating pathological thrombolic conditions by administering a compound of claim 1 which has inhibitory activity of factor X and/or factor VIIa, does not reasonably provide enablement for method of treating multi-organ failure, certain viral infections, cancer, myocardial infarction, respiratory distress syndrome etc. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to operate the invention commensurate in scope with these claims. Please note that treating coagulation event/thrombolic event in multiorgan failure patient is not treating the disease per se. The specification or art of record failed to provide descriptive and enabling support for such scope.

Claim 11 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making and using of specific prodrugs such as claims 12-13, does not reasonably provide enablement for any and all "produrg" (see Silverman). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. Please note that the particular prodrug conventionally employed for amino-containing drug does not offer descriptive and enabling support or operability to the entire complexed "prodrug" design.

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (f) he did not himself invent the subject matter sought to be patented.

Claims 1-6, are rejected under 35 U.S.C. 102(f) as being anticipated by ***CA:136:210039*** when D is N and ringD is bicyclic, the compounds are thrombin inhibitors; ***CA120:269926*** when D is N, and ringD is monoheteroatom and monocyclic 5-membered, the compounds are antibiotics; ***CA 91:193292*** when D is N, ringD is multiple heteroatoms monocyclic 5-membered, the compounds are hypolipemic agent; ***CA137:201331*** when D is C, ringD is monocyclic cycloalkyl, the compounds are dopamine receptor ligands; ***CA 132:279106*** when D is O, the compounds are GnRH inhibitor.

Please note that the attached registry compounds of each reference anticipated the claims as explained supra. Therefore, the issue of who is the first to invent such inventive concept as found in CA 136:2110039, CA 120:269926, CA 91:193292, CA137:201331, CA 132:279106, for which the specification did not disclosed but are evidenced that "another" was in possession of the claims.

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

(A)

Claims 1-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Beight et al. US.6,417,200 in view of Klein et al. US 2002/0016339.

Determination of the scope and content of the prior art (MPEP §2141.01)

Beight et al. '200 disclosed antithrombotic compounds, prodrugs, compositions, and method of structurally similar compounds.

Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)

Beight et al. '200 disclosed all the elements of the claims **except** the compounds are position isomer without an alkylene linker (see col. 47-48, examples 35-36). Klein et al.'339 taught that in similar antithrombotic compounds, 3- or 4-substitution on the piperidinyl ring and

insertion of a substituted alkylene chain between rings are optional choices for such compounds (seep.12-13 both 3-substituted and 4-substituted with alkylene insertion)

Finding of prima facie obviousness---rational and motivation (MPEP§2142-2143)

One having ordinary skill in the art would find the instant claims prima facie obvious **because** the skilled person is deemed to be aware of all the pertinent art in the field. The Beight et al. '200 and Klein '339 placed the optional choices of substitution at three or four position compounds and the modification by inserting alkylene chains in the possession of artisan in the field. The modification of one known compound i.e. Ackerman '436 with attributes of another known compound i.e. Klein '339 is prima facie obvious. One would have been suggested by the explicit examples with reasonable expectation of such modified compounds would have similar activity as the two antithrombotic compound references.

(B)

Claims 1-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klein et al. US 2002/0016339 in view of Beight et al. US 6,417,200.

Determination of the scope and content of the prior art (MPEP §2141.01)

Klein et al. '339 disclosed analogous compounds, prodrugs, compositions and method of inhibiting factor Xa and structurally similar species are disclosed on pages 12-13 (see 4-substituted compounds).

Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)

Klein et al. '339 disclosed all the elements of the claims **except** the species disclosed are those proviso i.e. one of Q, Q' and X is not bond. Beight '200 taught in analogous compounds that the insertion of a linker is optional choice for such compounds (see col. 3 lines 40-45) and particular variation of linkers were exemplified (see example 9, bond as linker, example 32-33, alkoxy as linker, example 35-36, amide as linker).

Finding of prima facie obviousness---rational and motivation (MPEP§2142-2143)

One having ordinary skill in the art would find the instant claims prima facie obvious **because** the skilled person is deemed to be aware of all the pertinent art in the field. The Klein '339 and Ackerman '436 placed the claimed compounds with optional choices of with or without linker in the possession of artisan in the field. The modification of one known compound i.e. Klein et al. '339 with attributes of another known compound i.e. Ackermann '436 is prima facie obvious. One would have been suggested by the explicit examples with reasonable expectation of such modified compounds would have similar activity as the two antithrombotic compound references.

7. The elected species wherein one of Q or Q' is not bond and X is an alkylene of C_{2-6} is neither anticipated nor rendered obvious by the art of record since the linker variation corresponding to Q-X-Q' is limited to two chain members (see Beight example 9, bond as linker, example 32-33, alkoxy as linker, example 35-36, amide as linker).

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celia Chang whose telephone number is 703-308-4702. The examiner can normally be reached on Monday through Thursday from 8:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner can be reached by facsimile at (703) 308-7922 with courtesy voice message supra.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

Celia Chang
Primary Examiner
Art Unit 1625

OACS/Chang
April 14, 2003